Original articles

"Natural histories" of mitral valve prolapse. Influence of patient selection on cardiovascular event rates

Alfredo Zuppiroli, Fabio Mori, Silvia Favilli, Alberto Dolara, Mary J. Roman*, Dawn Fishman*, Richard B. Devereux*

*II Cardiology Unit, Hospital of Careggi, Florence, Italy, *Department of Medicine, The New York Presbyterian Hospital-Weill Cornell Medical Center, New York, NY, USA*

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Background. **In previous studies the reported incidence of cardiovascular events among mitral valve prolapse patients has differed more than 10 fold. We endeavored to determine the relation between the clinical features and mode of ascertainment of mitral valve prolapse and the resulting event rate.**

Methods. **Between January 1979 and August 1996, 275 patients (129-47% men, 146-53% women, mean age 43 ± 19 years), were followed for a mean of 98 months after evaluation in a referral center for valvular heart disease. Comparative data were obtained from a separate, less selected population consisting of 316 patients.**

Results. **A total of 65 events occurred (2.9/100 patient-years): 46 (2.0/100 patient-years) mitral surgery, 12 cardiac deaths (0.5/100 patient-years), 6 neurologic ischemia (0.26/100 patient-years), and 1 infective endocarditis (0.04/100 patient-years). The overall event rate varied significantly according to demographic, clinical and echocardiographic variables (all $p < 0.0001$). It was higher among males (odds ratio-OR 2.1), subjects ≥ 45 years of age (OR 14.7), those with a holosystolic murmur (OR 25.9), an enlarged left ventricle (OR 13.5) or left atrium (OR 34.9) and those with 3-4+ mitral regurgitation at color Doppler echocardiography (OR 40.0). It was lower in those with an audible mid-systolic click (OR 0.05). These ORs closely resembled those we reported previously in a less selected population. At multivariate analysis, male gender ($p = 0.013$), severe Doppler mitral regurgitation ($p = 0.0048$), and left atrial enlargement ($p = 0.046$) were all independent predictors of events.**

Conclusions. **In a population of mitral valve prolapse patients, including many with significant mitral regurgitation at baseline, we identified similar predictors of events but an overall event rate nearly 3 times higher than that we previously reported for relatively unselected patients or family members in New York City (1/100 patient-years). Therefore, the impact of patient selection on the prevalence of mitral regurgitation, older age and male gender strongly affects the adversity of the "natural history" of mitral valve prolapse.**

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Address:

Dr. Alfredo Zuppiroli

Unità Operativa di Cardiologia 2 Azienda Ospedaliera Careggi Viale Pieraccini, 17 50139 Firenze

Mitral valve prolapse (MVP), the commonest form of valvular heart disease in industrialized countries[1,2], is inherited in an autosomal dominant mode[3-5]. After initial exclusion of linkage to the collagen[6,7] and other candidate genes, evidence has recently been obtained of linkage of dominantly inherited MVP to a region on chromosome 16p[8].

In contrast with this progress in elucidating the genetic etiology of MVP, considerable uncertainty concerning the prognosis of individuals with this condition persists. Reported rates of cardiovascular events have ranged from 0.3 to 3.7/100 patient-years[9-16] suggesting different "natural histories" of MVP. In addition to the varying incidences of events, longitudinal studies have reported different predictive values of baseline findings. For instance, in some studies auscultatory findings[10] or age[11] have been significant risk factors but they were not in others[12,14].

On the basis of the above, the present study was undertaken in order to assess the incidence of MVP-related events in patients prospectively evaluated in a referral center for valvular heart disease. The prognostic significance of readily available demographic, clinical and echocardiographic findings was determined and results were compared to those of a previously reported 8.5 year fol-

low-up of a population of relatively unselected individuals with MVP including index cases and affected relatives in a large family study[16].

Methods

Between January 1979 and August 1996 a total of 275 MVP patients were enrolled in this study and followed for a mean of 98 ± 52 months (range 10-216 months) before the occurrence of events or until their latest follow-up. At baseline evaluation, their mean age was 43 ± 19 years (range 7-81 years); 146 (53%) were women and 129 (47%) were men. All patients had echocardiographically documented MVP and none were recruited for purposes of screening or family study. Patients were referred for evaluation of palpitations in 95 cases (35%), dyspnea in 44 (16%), dizziness in 15 (5%), auscultatory findings in 72 (27%), previous cerebral ischemia in 9 (3%), fever of unknown origin in 6 (2%), and for clearance for high-level sports activity in 3 cases (1%). In 31 cases (11%), the indication for evaluation was not specified. Auscultatory findings of MVP (mid-systolic click, late-systolic murmur, and holosystolic murmur) were elicited by physical examination in multiple positions and with isometric exercise[17,18]. All patients were submitted to M-mode echocardiography performed according to the recommendations of the American Society of Echocardiography[19]. A diagnosis of MVP was made when the displacement of clear mitral leaflet interfaces posterior to the C-D line was ≥ 2 mm in late systole or, for holosystolic MVP, ≥ 3 mm[3,18,20]. Mitral leaflet billowing into the left atrium was revealed at two-dimensional echocardiography performed since 1980. The parasternal or apical long-axis views were employed[18,21]. Color Doppler echocardiography, performed since 1986, was used to grade mitral regurgitation according to the classification by Cooper et al.[22].

MVP-related events included cardiac death (either sudden or due to congestive heart failure), mitral valve surgery for progressive mitral regurgitation, cerebral embolic events, and infective endocarditis. Information about deceased patients was obtained from their relatives and physicians. All surviving patients were submitted to follow-up including clinical evaluation performed at least once during the study period.

Statistical analysis. Mean values are given ± 1 SD. The significance of mean differences between the two groups was examined by the unpaired Student's t-test. Differences in the incidence of events between groups, defined *a priori* as in our previous study[16], by gender (male or female), age (< 45 vs ≥ 45 years), presence or absence of specific auscultatory findings, and left heart chamber enlargement and grade of mitral regurgitation, were compared by the two-tailed Fisher's exact test. Left ventricular enlargement was defined as an end-diastolic diameter ≥ 60 mm; left atrial enlargement was defined as an end-systolic diameter ≥ 40 mm. Mitral regurgitation was considered severe if, using color Doppler criteria, it was graded 3+ or 4+[22]. Among baseline age, gender, auscultatory findings and echocardiographic signs of mitral regurgitation, independent predictors of complications were identified using forward stepwise multiple logistic regression analysis. Additional exploratory analyses considered the potential predictive value of overweight (body mass index > 26 kg/m^2) or hypertension (blood pressure > 140/90 mmHg) for cardiovascular events. Patients with multiple events were counted only once in both univariate and multivariate analysis.

Results

Subject characteristics. At baseline evaluation, auscultation revealed a mid-systolic click associated with a late-systolic murmur in 40 patients (15%), a mid-systolic click alone in 101 (37%), a late-systolic murmur alone in 42 (15%), and a holosystolic murmur in 70 patients (25%). Five patients (2%) had non-specific murmurs occurring in mid-systole and 17 subjects (6%) had auscultatorily silent MVP.

Echocardiography revealed a late-systolic prolapse in 245 patients (89%); 30 patients (11%) with two-dimensionally-verified holosystolic prolapse had auscultatory findings similar to the remaining patients. Women were younger than men (mean age 39 vs 48 years, $p < 0.00001$), were more likely than men to report palpitations (48 vs 33%, $p < 0.02$) and to have a mid-systolic click (71 vs 33%, $p < 0.00001$), were less likely to have a holosystolic murmur (13 vs 41%, $p < 0.00001$), and had a lower blood pressure (mean 125/76 vs 135/82 mmHg, $p < 0.00001$) and body mass index (mean 20.4 vs 23.2 kg/m^2, $p < 0.00001$). They did not differ with regard to other symptoms, auscultatory findings or heart rate. Among 185 patients evaluated by color Doppler, 67 (25% women) had 3+-4+ regurgitation and 119 (56% women, $p < 0.001$) had milder or absent mitral regurgitation.

Follow-up. Follow-up until the occurrence of MVP-related events or until the last event-free contact ranged from 10 to 216 months (mean 98 ± 52 months) for a total of 2245 patient-years. Follow-up was longer in women than in men (mean 107 vs 89 months, $p < 0.01$), and in the group with as opposed to that without a mid-systolic click (mean 111 vs 90 months, $p < 0.00001$); it was shorter in patients with a holosystolic murmur (mean 75 vs 106 months, $p < 0.00001$), or with 3+-4+ mitral regurgitation (mean 53 vs 77 months, $p < 0.00001$) as well as in patients ≥ 45 years old vs younger ones (mean 81 vs 114 months, $p < 0.00001$).

Cardiovascular events. During follow-up, 65 major morbid or mortal events occurred in 57 patients. Thus the event rate was 2.9/100 patient-years. Twelve patients died of cardiac causes, 2 within 24 hours of mitral

surgery, 2 of cerebral bleeding during anticoagulant therapy after mitral valve replacement, and 1 patient died of acute pulmonary edema 1 year after valve repair. Seven other patients died of cardiovascular causes without having undergone mitral surgery (4 suddenly, 2 of stroke and 1 of congestive heart failure). The overall incidence of cardiovascular death was therefore 0.5/100 patient-years. Three other patients died of non-cardiac causes (pancreatitis, colon cancer, and liver cirrhosis).

In 6 cases, a major cerebral event developed (0.26/100 patient-years): 4 transient ischemic attacks and 2 fatal strokes. One patient developed infective endocarditis (1/2500 patient-years).

During follow-up 46 patients underwent mitral surgery due to symptomatic progressive mitral regurgitation or to impaired left ventricular function (2.0/100 patient-years). Criteria for surgical referral among the 24 patients who were submitted to mitral valve reconstruction and among the 22 who were submitted to mitral valve replacement were similar.

Relation of events to baseline findings. The proportion of patients with cardiovascular events among men was twice that among women and that among overweight (body mass index ≥ 26 kg/m^2) 3 times that among normal-weight individuals (Table I). Stronger predictors (with odds ratios-OR ranging from 13 to 40) included older age, left ventricular hypertrophy (diagnosed as left ventricular mass/body surface area > 116 g/m^2 in men and > 104 g/m^2 in women[23]) and clinical and echocardiographic signs of significant mitral regurgitation. Adjustment of left ventricular chamber size for the impact of body size only modestly decreased the association between left ventricular dilation (left ventricular end-diastolic diameter/body surface area ≥ 32 mm/m^2) and events (OR 7.8, p < 0.00001). At univariate analysis the baseline blood pressure was significantly higher in the group with subsequent events vs that without (average systolic blood pressure 137 ± 16 vs 127 ± 17 mmHg, p < 0.0005; average diastolic blood pressure 82 ± 10 vs 78 ± 9 mmHg, p < 0.03).

Multiple logistic regression analysis including variables which identified significant mitral insufficiency either clinically (holosystolic murmur) or echocardiographically (left ventricular and atrial enlargement, Doppler-graded regurgitation), gender and age as a categorical variable (≥ or < 45 years) was performed. In this analysis, male gender (p = 0.013), Doppler-documented 3+ or 4+ mitral regurgitation (p = 0.0048), and left atrial enlargement (p = 0.046) were independent predictors of MVP-related events. Using either an enter procedure in which the considered variables are forced into the model or else forward or backward stepwise regression, co-linearity was modest; gender and echo-diagnosed mitral regurgitation remained highly significant predictors of events, with only slight significance for left atrial enlargement. Further analyses, in which the systolic blood

Table I. Prediction of mitral valve prolapse events by baseline findings.

Variable	Proportion with events	OR (95% CI)	p
Gender		2.1 (1.2-3.8)	0.0017
Male (47%)	35/129 (27%)		
Female (53%)	22/146 (15%)		
Age (years)		14.7 (6.0-35.7)	< 0.00005
≥ 45 (48%)	51/131 (39%)		
< 45 (52%)	6/144 (4%)		
Mid-systolic click		0.05 (0.02-0.14)	< 0.00005
Present (51%)	5/140 (4%)		
Absent (49%)	51/135 (38%)		
Holosystolic murmur		25.9 (12.1-55.4)	< 0.00005
Present (26%)	44/73 (60%)		
Absent (74%)	12/202 (8%)		
Left ventricular diameter (mm)		13.5 (6.7-27.1)	< 0.00005
≥ 60 (26%)	38/72 (53%)		
< 60 (74%)	17/203 (8%)		
Left atrial diameter		34.9 (13.1-92.9)	< 0.00005
≥ 40 (37%)	50/103 (49%)		
< 40 (63%)	5/172 (3%)		
Mitral regurgitation		40.0 (13.2-121.4)	< 0.00005
Grade ≤ 2 (64%)	4/119 (3%)		
Grade 3 and 4 (36%)	39/67 (58%)		
Body mass index (kg/m^2)		3.2 (1.3-8.1)	0.0205
≥ 26 (8%)	9/21 (43%)		
< 26 (92%)	48/254 (19%)		
Left ventricular hypertrophy		13.1 (5.7-30.3)	< 0.00005
Present (35%)	33/64 (52%)		
Absent (65%)	9/120 (8%)		

CI = confidence interval; OR = odds ratio.

pressure or body mass index were considered, demonstrated that these variables did not independently add to the prediction of events. Cox regression analysis with age, gender and body mass index as covariates, revealed progressive separation between patients with 3+ or 4+ mitral regurgitation and those with milder or absent regurgitation throughout the period of follow-up (Fig. 1).

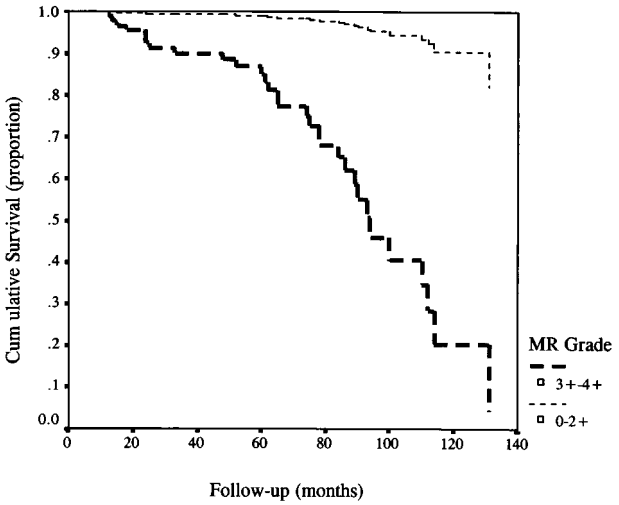

Figure 1. *Survival free of cardiovascular events* (vertical axis) *was lower (p < 0.0001) in patients with moderate to severe mitral regurgitation (MR) than with milder or absent regurgitation throughout the duration of follow-up* (horizontal axis).

Because the strong effect of 3+-4+ mitral regurgitation on event rates might obscure predictors of events in individuals with mild or no regurgitation, further analyses were performed in the latter group. In this group, those who experienced MVP-related events during follow-up differed from the remainder with regard to age (mean 59 vs 38 years, p = 0.017) and to weight (mean body mass index 26.7 vs 21.0 kg/m^2, p = 0.002). Differences in gender, blood pressure, auscultatory findings and echocardiographic measurements were not statistically significant. In view of the small number of MVP patients with events in this low-risk group, multivariate analyses were not performed.

Comparison of results in the Florence and New York series. Tables II and III show comparisons of major events and of predictors of events respectively between the present and previous study[16]. The rate of events was nearly 3-fold higher in the present study (Table II). Rates of cerebral ischemia, infective endocarditis and of cardiac and non-cardiac death in the Florence and New York City cohorts were statistically indistinguishable. However, the rate of mitral surgery was substantially higher in the Florence population.

Male gender and manifestations of severe mitral regurgitation at baseline examination were more prevalent in the Florence series than in the New York City cohort (Table III). However, these variables had similar rela-

Table II. Comparison of major events in the present and previous studies.

Type	No. events		Rate per 100 patient-years (95% CI)	
	Florence (n=275)	New York[16] (n=316)	Florence (2245 patient-years)	New York[16] (2646 patient-years)
Mitral surgery	46	11	2.0 (1.5-2.6)	0.4 (0.1-0.7)
Cardiac death	12	6	0.5 (0.2-0.8)	0.2 (0.04-0.4)
Neurologic ischemia	6	7	0.3 (0.05-0.5)	0.3 (0.07-0.5)
Infective endocarditis	1	2	0.04 (-0.04-0.1)	0.1 (-0.03-0.2)
All cardiovascular events	65	26	2.9 (2.2-3.6)	1.0 (0.6-1.4)
Non-cardiac death	3	7	0.13 (-0.02-0.3)	0.3 (0.07-0.5)

CI = confidence interval.

Table III. Comparison of predictors of events in the present and previous studies.

Type	Prevalence of predictor (95% CI)		OR (95% CI)	
	Florence	New York[16]	Florence	New York[16]
Male gender	47% (41-53)	30% (25-35)	2.1 (1.2-3.8)	2.4 (1.0-5.9)
Age ≥ 45 years	48% (42-54)	42% (37-49)	14.7 (6.0-35.7)	4.0 (1.5-10.5)
Mid-systolic click	51% (45-56)	56% (51-62)	0.05 (0.02-0.14)	0.26 (0.1-0.6)
Holosystolic murmur	26% (21-32)	4% (2-6)	25.9 (12.1-55.4)	27.0 (7.6-95.0)
Left ventricular diameter ≥ 60 mm	26% (21-31)	7% (4-9)	13.5 (6.7-27.1)	15.8 (5.5-45.2)
Left atrial diameter ≥ 40 mm	37% (32-43)	8% (5-11)	34.9 (13.1-92.9)	15.4 (5.7-41.3)

Abbreviations as in table I.

tive risks for events in both series. In the present study, the estimated relative risk for events was higher for older age and lower for the presence of a mid-systolic click.

Table III also shows that the 95% confidence intervals for the prevalence of age ≥ 45 years and a mid-systolic click in the two populations overlap while those for the prevalence of male gender or for manifestations of significant mitral regurgitation do not. In the present study, the 95% confidence intervals for the ORs for events associated with each predictor overlap in the two populations with the exception of a stronger positive predictive value for age ≥ 45 years and a stronger negative predictive value for an audible mid-systolic click.

Pooled univariate analysis of the two populations (total n = 591) showed a substantially higher rate of events in the Florence population (OR 3.5, 95% CI 2.1-5.9, p < 0.00005) with progressive separation in life-table analysis (Fig. 2)[16]. However, the center effect did not even approach statistical significance when it was entered as an indicator variable together with other predictor variables in a multiple logistic regression. The presence of a holosystolic murmur at baseline was a particularly strong predictor of an adverse outcome as assessed by either Kaplan-Meyer life-table (Fig. 3) or Cox proportional hazard (Fig. 4) analysis. When the Florence and New York populations were pooled, the complication-free survival was similar in the two centers among subgroups with (Fig. 5) or without (Fig. 6) a holosystolic murmur.

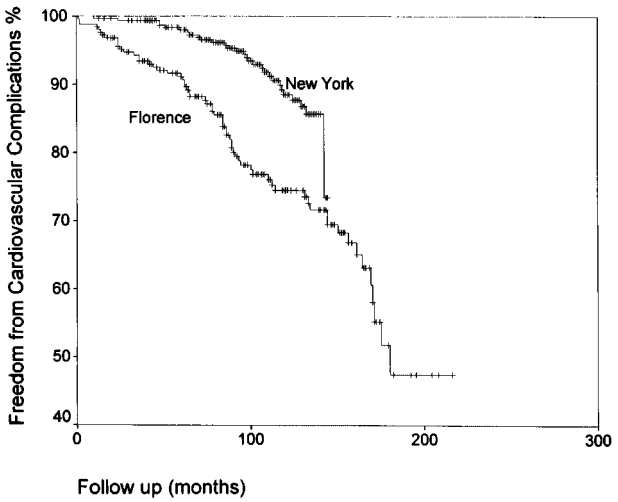

Figure 2. *Survival free of cardiovascular events* (vertical axis) *was lower in the present population than in a previously studied population from New York[16].*

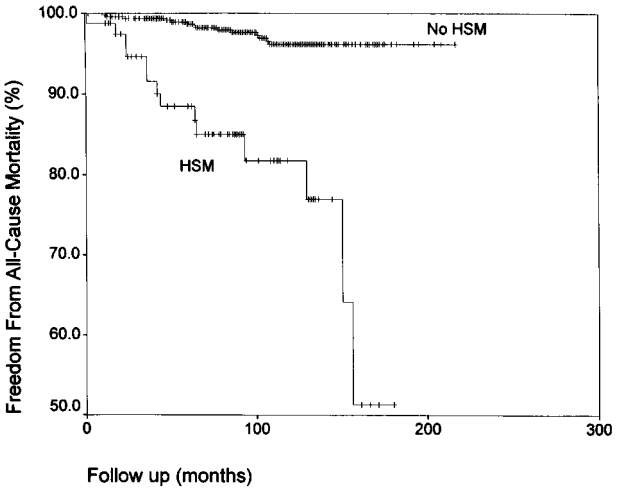

Figure 3. *Kaplan-Meyer curves showing that, during follow-up, freedom from all-cause mortality* (vertical axis) *was significantly lower (p < 0.0001) in patients with than in those without a holosystolic murmur (HSM).*

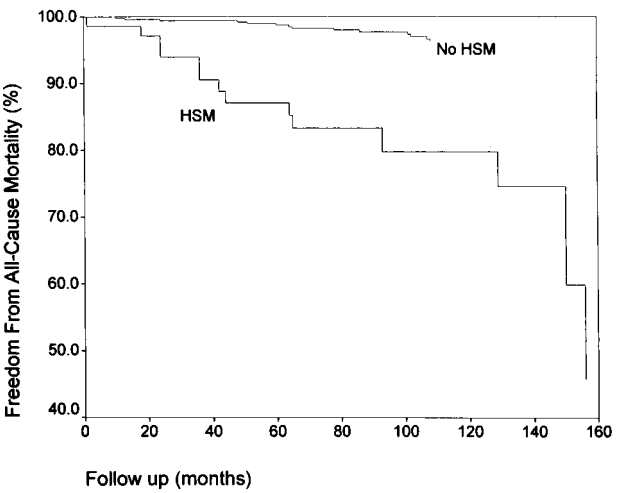

Figure 4. *Cox proportional hazards curves show that, during follow-up, all-cause mortality was significantly higher in patients without a holosystolic murmur (HSM).*

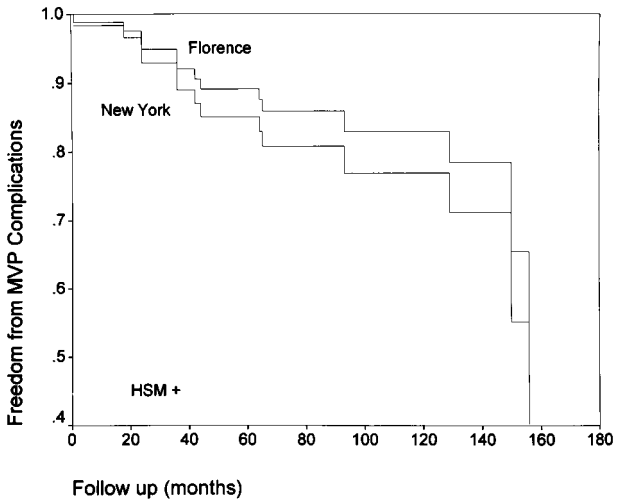

Figure 5. *Kaplan-Meyer curves showing similar event-free survival in mitral valve prolapse (MVP) patients from Florence and from New York with a holosystolic murmur (HSM).*

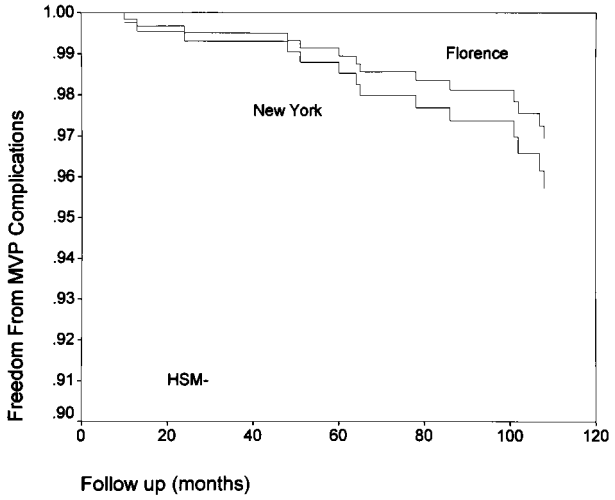

Figure 6. *Kaplan-Meyer curves showing similarly good event-free survival in mitral valve prolapse (MVP) patients from Florence and New York without a holosystolic murmur (HSM).*

Discussion

MVP has been associated with serious complications, including death, progressive mitral regurgitation requiring surgery, infective endocarditis and cerebral ischemic events[24-29]. While initial longitudinal studies of patients with an auscultatory-based diagnosis of MVP suggested a relatively low rate of MVP-related events[9-11], the event rates in some echocardiographically-based studies in the 1980s were substantially higher (Table IV)[9-14,16]. As shown in table IV, our present and previous[16] studies, with a greater number of patient-years of follow-up than any previous report, show a higher event rate in Florence than in New York. However, when clinical and echocardiographic predictors of events were entered in multivariate analyses, the center difference became insignificant. This suggests that the difference in event rate between the present and the previous reports[16] is largely explained by patient characteristics. The Florence MVP patients were observed in a referral center for the medical and surgical care of patients with valvular heart disease, in contrast to the previous population[16] of relatively unselected MVP patients including index cases and affected family members in the prospective Cornell MVP Family Study[4,18].

As shown in table I, the results of the present study confirm the previous observation[16] that older age, male gender and clinical and echocardiographic signs of mitral regurgitation are, at baseline evaluation, readily-available findings that identify MVP patients at a higher risk for events. Prognostic predictors and their ORs for events are quite similar in the patient series from Florence and New York (Table III). This suggests that in an inherited condition like MVP, one can obtain information about the predictors of events in relatively unselected persons with the condition by following relatives or spouses in whom MVP is detected in family studies that accurately predict event rates in more selected groups of patients, and that the converse is also true. Further evidence of the consistency of predictors of MVP-related events across different populations is the finding that older age and higher body mass index both predicted these events in low-risk patients without significant mitral regurgitation in the present series and in recent case-control and longitudinal analyses in a separate population[30].

In the patient population selected in Florence, the higher prevalence of clinical and echocardiographic signs of mitral regurgitation accounted for the more frequent occurrence of mitral surgery than in the New York City cohort. The incidence rates of other events were virtually identical. The observation that the incidence of cerebral ischemic events and of infective endocarditis was relatively low with respect to previous reports[12,14] is noteworthy. Our data thus confirm recent evidence[31] that neurologic ischemia does not constitute a frequent clinical problem in patients with MVP. The incidence of endocarditis was lower than in some previous reports; this was potentially attributable to the successful use of antibiotic prophylaxis in MVP patients with mitral regurgitation[32]. However, the point estimate of one endocarditis case per 2500 person-years is consistent with our previous estimate that the incidence of endocarditis among MVP patients is 8 times higher than in the general population (1 per 20 000 person-years)[26].

Table IV. Complications of mitral valve prolapse.

Reference	No. patients	No. events	Follow-up (years)	Incidence of events (%/year)	Patient-years
Allen et al.[9], 1974	62	8	13.8	0.9	856
Mills et al.[10], 1977	53	8	23.7	1.1	1256
Bisset et al.[11], 1980	109	2	6.9	0.3	752
Nishimura et al.[12], 1985	237	28	6.2	1.9	1469
Vered et al.[13], 1985	42	8	5.1	3.7	214
Duren et al.[14], 1988	300	62	6.1	3.4	1830
Zuppiroli et al.[16], 1995	316	26	8.5	1.0	2686
Present study	275	65	8.2	2.9	2245

As exemplified by the results of our present and previous studies[16], the performance of two studies by the same research group using the same methods and endpoints in differently selected populations can identify quite similar results concerning the prognostic predictors and respective ORs for the prediction of events despite striking differences in overall event rates. Thus, features of significant mitral regurgitation identified MVP individuals with an approximately 5% annual event rate (principally mitral valve surgery) in two populations with differing prevalences of predictors of high risk. Moreover, this study demonstrates that the risk of events in individuals with MVP is highly dependent on simple clinical and objective echocardiographic findings. These findings will facilitate correlation of the results of future genetic studies with the expected prognosis for the observed phenotype in MVP individuals under study.

Some limitations of this study merit consideration. First, the most common event in the present series of MVP patients was mitral valve surgery, the rate of which could be influenced by the criteria used for surgical referral. In both the Florence and New York populations, mitral valve replacement or repair was recommended when valvular regurgitation caused dyspnea or when left ventricular functional impairment was recognized. Second, the number of events in younger MVP patients or other lower-risk subgroups was insufficient to identify predictors of events therein. Further studies including larger numbers of MVP patients with a longer follow-up will be needed to remedy this situation. Third, data on mitral leaflet thickness or other morphologic predictors of high risk are unavailable in the Florence patient series. However, in the New York MVP population previously studied, we had not found any relation between mitral leaflet thickness and subsequent event rate[33]. Finally, the strong association we observed in MVP patients between established mitral regurgitation and subsequent events may be applicable to mitral regurgitation of other etiologies. Further studies in other populations will be needed to address this question.

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